Poster Presentations - Session II

AUTOIMMUNE

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TREATMENT OF SEVERE MULTIPLE SCLEROSIS WITH MELPHALAN AND TOTAL LYMPHOID IRRADIATION FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION

Ferreira, A.[1]; Miller, W.E.[1]; Andrey, J.W.[1]; McMillan, R.[2]; Tripuraneni, P.[1]; Romine, J.S.[1]; Sipe, J.C.[1]; Burian, C.[1]; Mason, J.R.[1] 1. Scripps Clinic, La Jolla, CA; 2. The Scripps Research Institute, La Jolla, CA

Objective: To evaluate the safety and therapeutic efficacy of melphalan and TLI followed by autologous CD34+ selected stem cells for patients with primary or secondary progressive multiple sclerosis. Methods: Peripheral blood stem cells were mobilized with cyclophosphamide at 1.5 g/m^2 and G-CSF 10 µg/kg/day beginning 24 hours after cyclophosphamide until completion of stem cell harvesting. Products were CD34 selected using Isolex 300i. Transplant preparative regimen consisted of high dose melphalan at 140 mg/m^2 IV over 30 minutes on day -4 and TLI 300 cGy bid on days -2 and -1 with stem cell infusion on day 0. G-CSF (5 µg/kg sc) was administered from day 0 until ANC > 1500/µl for 3 consecutive days. Results: Eight patients with severe multiple sclerosis and a median age of 45 (range 32 to 56) have been enrolled in the study. Neutrophil (ANC > 500) and platelet (> 100,000) recovery occurred by day 9 (range 8 to 10) and day 17 (range 15 to 20), respectively. A median of 2 red cell transfusions (range 0 to 2) and a median of 2 (range 1 to 2) single donor units of platelets were required. The median number of CD34 positive cells x 10^6/kg collected and infused was 10.9 (range 4.5 to 25.9) and 8.2 (range 4.5 to 12.9). The median number of T cells (CD3) x 10^4/kg infused was 9.9 (range 1.4 to 52.6). No grade 3-4 non-hematologic toxicity was observed. Transient neutropenic fever occurred in 2 patients, one patient developed microscopic hematuria and had a positive urine culture for BK virus. Day 100 survival was 100%. Conclusion: Overall, the toxicities from high dose melphalan and TLI have been minimal confirming that this regimen is a feasible and safe treatment in patients with severe multiple sclerosis. Further follow up is required to assess the benefits of this therapy.

AUTOLOGOUS

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HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ACUTE MYELOID LEUKEMIA IN REMISSION

Ball, E.D.; Davis, B.N.; Holman, P.; Basbey, A.; Carrier, E.; Chen, J.; Kormanik, P.; Corringham, S. UCSD Medical Center, San Diego, CA

Peripheral blood stem cell transplantation (PBSCT) is increasingly employed as consolidation therapy for patients with standard to high-risk acute myeloid leukemia (AML) in first remission. We report on 9 AML patients who underwent an autologous PBSCT between May, 2000 - June, 2001, using a modification of the regimen reported by Linker (Biol. of Blood and Marrow Trans. 6:50-57, 2000) to lower toxicity for the relatively mature patients seen at our center. After achieving remission with cytosine-arabinoside-based induction, 8/9 patients underwent consolidation with cytarabine (2 g/m^2 every 12 hours) and etoposide (10 mg/kg/day) for 3 days (reduced from 4 days). One patient received the 4 day regimen. All patients received the preparative regimen of intravenous busulfan (12.8 mg/kg) over 4 days and cytoxan (120 mg/kg, IV) over 2 days. Four patients were diagnosed with FAB subtype M2, 3 with M5, 1 with M4, and 1 with M6. At diagnosis, cytogenetics were normal for 6 patients and abnormal for 3 patients [46XX, der (19) t(11;9) (q13,q13); 46X, t(9;22) (q34;q11.2); 45X, -Y(3)/ 46XY,(cp16)]. The median WBC count at diagnosis was 59.7 (x10^9 /L). All patients were in complete remission (CR) (CR1: 7; CR2: 2) at the time of transplant. The median age of all patients was 61 years (range 22-70). The median CD34+ cell dose infused was 5.46 (x10^6/kg). There were no treatment-related deaths nor cases of hepatic veno-occlusive disease. Four patients relapsed at a median of 4.1 months post-PBSCT (1 in CR2, 3 in CR1). Five patients remain in CR at a median of 9.6 months post-PBSCT. This retrospective study in relatively mature AML patients, many with high-risk features, demonstrates the safety of the modified regimen (reduced dose of ara-C and etoposide, intravenous Bu) and provides an alternative to non-stem cell supported repetitive consolidation regimens for this population of patients.

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ONCE DAILY INTRAVENOUS BUSULFAN (BUSULFEX) AND CYCLOPHOSPHAMIDE FOLLOWED BY STEM CELL TRANSPLANT FOR HEMATOLOGIC MALIGNANCIES: DOSING MODIFICATION PROTOCOL

Day, S.D.[1]; McGuirk, J.P.[1]; Picken, S.[1]; Reed, M.[2]; Copelan, E.A.[3]; Leather, H.L.[4]; Wingard, J.R.[4]; Geller, R.B.[5]; Abhyankar, S.[1]; Lennon, S.[6] 1. Oncology and Hematology Associates of Kansas City, Kansas City, MO; 2. Case Western University, Cleveland, OH; 3. Ohio State University, Cleveland, OH; 4. University of Florida, Gainesville, FL; 5. University of Arizona, Phoenix, AZ; 6. Orphan Medical, Minnetonka, MN

In a five cohort escalation protocol, we sought to determine the safety, efficacy, and PK profile of once daily IV busulfan (IVBu) combined with cyclophosphamide (CY), and thus, the feasibility of outpatient administration of this regimen. Twelve hospitalized pts (NHL=6, AML=2, CML=1, MDS=1, HD=1, MM=1; autoPBSCT=8, alloPBSCT=4) received IVBu for 4 days followed by CY 60mg/kg/d IV for 2 days. In cohort 1, 4 pts received IVBu 1.6mg/kg over 4h q12hx2, then 0.8mg/kg over 2h q6hx12. In cohort 2, 4 pts received IVBu 1.6mg/kg over 2h q12hx2, then 1.6mg/kg over 4h q12hx2, then 0.8mg/kg over 2h q6hx8. In cohort 3, 4 pts received IVBu 3.2mg/kg over 4h q24hx1, then 1.6mg/kg over 2h q12hx2, then 0.8mg/kg over 2h q6hx8. Multiple timed blood samples from first and last days of IVBu were analyzed centrally for busulfan concentration by gas chromatography. Pts achieved an ANC>500 and plt>20K by median day 13.5 (10-19) and day 16.5 (13-50), respectively. No pt experienced toxicities limiting cohort escalation. One pt in cohort 2 developed moderate VOD on day 18 that resolved by day 53. Toxicities were mild to moderate and included nausea, vomiting, diarrhea, mucositis, and increased LFTs. With median follow-up of 193d (61-370d), 2 pts have expired (relapse on d203 and GVHD on d207). PK data (expressed as mean ± std. dev. below) are linear, demonstrate proportional increases in AUC, and are associated with limited variability. We continue to enroll pts with the last cohort scheduled to receive IVBu 3.2mg/kg/d IV q24hx4. Dose modification of IVBu appears safe, effective, and feasible for outpatient administration.

Cohort	N	AUC (µMol.min) - q6h dose	AUC (µMol.min) - q12h dose	AUC (µMol.min) - q24h dose
1	4	1456±738	2276±673	NA
2	4	1086±88	2252±155	NA
3	4	1293±144	NA	5172±580

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PREDICTING SUCCESSFUL PERIPHERAL BLOOD STEM CELL (PBSC) COLLECTION USING PERIPHERAL WBC AND CD34+ CELL COUNTS: A COST ANALYSIS

Heller, B.J.; Ornstein, D.L.; Hensley, R.; Ririe, D.W.; Shaughnessy, P.J.; Bee, C.; Reilly, P.A. Wilford Hall Medical Center, Lackland AFB, TX

Background: Collection of sufficient PBSC for engraftment using the fewest leukapheresis sessions possible serves to minimize

patient risk and overall expenditure. Peripheral blood (PB) WBC count has been shown to be a poor indicator for successful PBSC collection, whereas PB CD34+ cell count may be a more reliable predictor. We undertook this study to determine the use of PB CD34+ cell counts to optimize the timing of PBSC collection. Methods: Consecutive PBSC donors (n = 163) were mobilized using growth factors and chemotherapy. PB WBC and PB CD34+ cell counts were determined with each leukapheresis session and the total CD34+ cell count was determined for the leukapheresis product (LP) from each session. The following correlations were then obtained: PB WBC and PB CD34+ cell counts, PB WBC and LP CD34+ cell counts, and PB CD34+ and LP CD34+ cell counts. Results: There was a poor correlation between PB WBC and LP CD34+ cell counts (r = 0.21). There was a significant correlation, however, between PB CD34+ and LP CD34+ cell counts (r = 0.70). When successful leukapheresis was defined as a collection of a LP containing 2.0 x 106 CD34+ cells/kg recipient body weight, the PB CD34+ but not the WBC count predicted successful collection. The table gives percentage of successful collections in one session. Additionally, the use of peripheral CD 34+ count to predict successful collection would provide a cost savings of approximately $45,000 per 100 patients.

PB CD34+ Count/µl	PB WBC/µl	Percentage of Successful Collection in Single Leukapheresis Session
≥26		83
≥34		89
	≥5	45
	≥10	47
	≥25	54

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SUPPORTIVE CARE REQUIREMENTS OF AUTO & MATCHED SIBLING TRANSPLANT RECIPIENTS IN THE FIRST 30 DAYS POST TRANSPLANT

Sangam, S.; Dorr, S.; Garner, P.; Akhtar, A.; Momin, F. Oakwood Hospital, Dearborn, MI

Purpose: To quantify transfusion, nutritional support, antibiotic and cytokine requirements of stem cell transplant (SCT) recipients in the first 30 days post SCT. Methods: 54 autografts and 20 allografts were studied from day of admission to day +30 post SCT. The following were the criteria for supportive care: Unless the patient was bleeding or unstable the following guidelines were followed. 1. Two units PRBC transfused for hemoglobin of 8 gms/dl or less. 2. Six units of random donor platelets transfused for a platelet count of 15,000 or lower. 3.Empiric antibiotics included Ceftazidime for febrile neutropenia. Vancomycin was added if warranted. 4. G-CSF was given from day +1 until the ANC was > 500 for 3 consecutive days. 5. TPN was initiated when PO intake was reduced and continued until oral intake was reestablished. 6. Hospital stay. Results: Of the 54 autografts 24 were done for Breast Cancer, 24 for hematological malignancies and 7 for testicular and Ovarian Cancer. Median age was 50 yr. (21 - 72). Twenty were males and 34 were female. There were 10 male and 10 female allogeneic recipients with a median age of 53 yr. (24 to 69). All allografts had myeloablative regimens. Conclusions: Uncomplicated autologous and allograft recipients treated on standard protocols using myeloablative regimens have a predictable hospital stay, requirement of transfusions, nutrition support, cytokine and antibiotics. Besides providing quality control and consistency, this data in combination with the cost of other drugs and laboratory tests could also aid in computing the initial cost of uncomplicated autologous and allogeneic stem cell transplantation.

	n	median RBC units	median platelet units	Median TPN days	Median Antibiotic days	Median G-CSF days	Median Hospital stay (days)
AUTO	54	4 (0 - 13)	12 (0 - 80)	5 (0 - 18)	9 (0-29)	12 (6 - 32)	18 (8 - 32)
ALLO	20	6 (2 - 20)	19 (6 - 182)	8 (0-43)	11(0-83)	14 (12 - 47)	26 (12-68)

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A PHASE II TRIAL OF HIGH DOSE CHEMOTHERAPY AND CONCURRENT RITUXIMAB FOLLOWED BY AUTOLOGOUS PERIPHERAL STEM CELL TRANSPLANTATION FOR TREATMENT OF RELAPSED CD20 POSITIVE B-CELL NON-HODGKIN'S LYMPHOMA

Vusirikala, M.; Stein, R.S.; Brandt, S.; Morgan, D.; Greer, J.; Jagasia, M.; Kassim, A.; Schuening, F.; Goodman, S. Vanderbilt University Medical Center, Nashville, TN

Introduction: High dose therapy (HDT) with autologous stem cell transplantation (ASCT) improves event-free survival in patients with relapsed NHL. However, 40-60% of patients subsequently relapse. An attempt to improve outcome after ASCT has been made by addition of Rituximab as adjuvant therapy. To date, several investigators have reported safe and effective use of Rituximab prior to stem cell collection (in-vivo purging) and/or at time of hematopoietic recovery following ASCT. Several studies have also observed cytoreductive synergism when Rituximab is administered concurrently with chemotherapy. The purpose of our phase II trial was to extend these observations of synergism to the HDC/ASCT situation. Methods: We treated 7 patients (M:F=3:4; median age at transplant=62 yrs) with NHL (diffuse large cell 3, transformed large cell 2, mantle cell 1 and follicular center cell grade-II 1) with ASCT. All patients received cyclophosphamide 7200mg/m2, BCNU 400mg/m2 and etoposide 2400mg/m2 (CBV) for conditioning and unpurged stem cells. Rituximab at 125mg/m2 was administered on days –6, -5, -4 and at 375mg/m2 on days +1, +8 and +15. Toxicity, survival and relapse were measured. Results: All 7 patients completed planned therapy. Median duration of follow up was 174 days (122-370). Engraftment was achieved in all patients with median day to ANC>500/µL of 13 days (10-18) and platelets>20,000/µL of 13 days (8-41). No patients developed grade III or greater non-hematologic toxicity. 2/7 patients developed persistent neutropenia (grade II-III) post-engraftment requiring G-CSF, 3/7 patients had delayed thrombocytopenia (grade II-III) and one patient had candida esophagitis after engraftment. All patients survived past 100 days post-transplant. 1/7 pts has relapsed and no deaths have occurred to date. Conclusion: Although the number of patients is small, our results demonstrate the safety of concurrent use of Rituximab with HDC. Longer follow up and larger randomized studies are required to prove efficacy of this treatment approach.

GRAFT PROCESSING

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A CD34 PREDICTION MODEL

Bakkestad-Legare, P.[1,2]; Tulloch, M.[1,2]; Giftakis, A.[1,2]; Hacking, K.[1,2]; Rubinger, M.[1,2] 1. Cancercare Manitoba, Winnipeg, MB, Canada; 2. Hematopoietic Stem Cell Lab, Winnipeg, MB, Canada

Blood CD34 has been performed in our centre since 1998 to determine the optimal apheresis timing of Peripheral Blood Progenitor Cells (PBPC) from autologous Blood and Marrow transplants (BMT) patients. Some centres sample the product for CD34+cells during apheresis in order to determine whether the PBPC product is sufficient. This practice may result in possible product contamination and increase resource time. Cell-kinetic models of predictive algorithm for Blood CD34 have been used to determine the CD34+/kg in the apheresis collection. Our centre retrospectively evaluated 38 patients who underwent 53 consecutive PBPC collections. Their diagnoses were Non-Hodgkin's lymphoma (N=14), Hodgkin's (N=9) and Multiple Myeloma (N=15). Blood CD34 and the CD34+/kg in the corresponding PBPC were analyzed using a CD34 prediction model (previously reported at ISHAGE June, 2001). The correlation was significant with a r2 value = 0.9890 and a p value = < 0.0001. A prospective study is underway using the CD34 prediction model to determine the volume of apheresis required to reach the desired CD34+/kg. To date, 14 patients have undergone 21 PBPC collections. Their

diagnoses were Non-Hodgkin's lymphoma (N=5), Hodgkin's disease (N=1) and Multiple Myeloma (N=8). All patients received chemo-mobilization and granulocyte colony stimulating factor (G-CSF), with the addition of stem cell factor for two patients. Blood CD34 is tested once the patient's counts white blood count is beginning to rise after nadir. Differences were noted between disease states and corresponding mobilizing chemotherapy. Collection efficiencies for the COBE Spectra, the apheresis machine used for PBPC collections are examined for each patient. Only 3 of 21 Apheresis products had a lower CD34+/kg than what was predicted. Using the CD34 prediction model, the required volume for apheresis to achieve the desired CD34+/kg cell dose can be specifically designed for each patient, thus allowing for an optimized collection.

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DOES ABO AND RH INCOMPATIBILITY BETWEEN DONOR AND RECIPIENT INFLUENCE GVHD INCIDENCE?

Barone, B.; Paiva, T.C.; Bouzas, L.S.; Barbosa, M.L.; Maciel, C.M.; Paraguassu-Braga, F.H.; Lerner, D.; da Matta, J.; Tavares, R.C.; Tabak, D.G. INCA, Rio de Janeiro, Brazil

The incompatibilities of the ABO blood system and the Rh imunophenotyping between donor and patient do not represent an obstacle condition to bone marrow transplantation (BMT), but the quality of patient's life can be greatly influenced by the severity of Graft-versus-host disease (GVHD), the most important BMT complication. This retrospective study was carried out with 65 transplanted patients from 1996 to 2000 that had any ABO blood (major or minor) and Rh incompatibility. Comparing the results to a group control with the same number of transplanted patients, whose donors were completely ABO and Rh compatible, we analyzed if this type of incompatibility was able to increase the GVHD frequency. The marrow products were processed with standardized methods and the imunohematologic typing was carried out using assay tubes with standard reagents. Nevertheless, GVHD frequency was increased in the group with ABO blood system incompatibility, considering the group control, this difference wasn't statistically significant: chronic GVHD was present in 32 patients (49,2%) with similar ABO system and in 39 individuals (60,0%) with any blood incompatibility (p = 0.2905); acute GVHD was found in 17 patients (26.2%) in the group control, against 24 patients (36.9%) with ABO blood system incompatibilities (p = 0.2574). Although complementary data, in a large number of individuals, would be necessary to confirm this findings, and knowing that other factors can directly increase the incidence of GVHD, the ABO system would be an auxiliary tool in the BMT donor selection process.

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CD34+ SELECTION OF PBSC AND BM BY IMMUNOMAGNETIC METHOD (ISOLEX 300I). EVALUATION OF THE SYSTEM, THE QUALITY OF PRODUCTS AND TUMOR DEPLETION

Desbois, I.[1]; Colombat, P.[2]; Roingeard, P.[3]; Degenne, M.[4]; Ducrot, T.[5]; Domenech, J.[4]; Georget, M.[4]; Lefevre, M.[1]; Binet, C.[4]; Delain, M.[2] 1. Cellular Therapy Lab - Centre Atlantique Blood Bank, Tours, France; 2. Dpt of Oncology - Univ Hospital, Tours, France; 3. Dpt of Microscopy - Univ Hospital, Tours, France; 4. Lab of Hematology - Univ Hospital, Tours, France; 5. Nexell International, Wemmel, Belgium

The purpose of this study was to analyse the efficiency of the automated system for CD34 selection in auto stem cells transplantation (ASCT) for NHL or CLL. ASCT support for HDC improves long term survival in those cases but the risk of reinfused tumor cells to the patients could participated to the releapse. CD34+ selection can improve the depletion in residual disease. From 1997 to 2001, 36 patients with low grade NHL and stage B or C CLL were transplanted with selected stem cells (Isolex 300i with 3 versions v1.12;v2.0b1;V2.5) from PBSC (n=18) or BM (n=18). The selection was done just after collection for PBSC and on the ficolled fraction for BM. After selection, the mean purity was 98.8% for PBSC and 91.1% for BM. The overall yield obtained was at 54.5% for PBSC and 44.2% for BM with a significant increase with the latest version (respectively 63.3% and 74.6%). In conclusion, the Isolex system can provide a very high purity in CD34+ cells. The yield was better when PBSC were selected in comparison with BM probably because of a higher cellular homogeneity. We have also obtained better performances with the version 2.5 of the Isolex. For each PBSC, we have obtained a good quality of products in terms of CD34+/Kg and CFU GM (results will be described). Regarding the tumoral depletion, our results are really encouraging and more particularly for CLL.

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HIGHER FREEZING CONCENTRATIONS AND ENGRAFTMENT

Dozier, M.M.; Dicke, K.A.; Gandy, J.; Patel, M. Arlington Cancer Center, Arlington, TX

At Arlington Cancer Center, we analyzed reinfusions on 20 patients (14 breast cancer, 3 NHL, 1 Hodgkin's lymphoma, 1 Multiple Myeloma and 1 AML) between 1999-2000 were analyzed for final CD34 x 10*6 cells/kg, WBC concentration of the frozen apheresis product and the effect WBC concentration had on days to ANC recovery to 500 cells/mm3 and platelet recovery to 20,000/mm3. Reinfusions were usually administered over two consecutive days with standard of care antibiotic and antifungal support. The median WBC concentration x 10*6/ml was 510 (183-890). There was no significant difference between days to ANC recovery or platelet recovery between reinfusions of products frozen at > 500 x10*6 WBC/ml(N=18 reinfusions) and products frozen at < 500 x10*6 WBC/ml(N=12 reinfusions), (14+4 days vs 13+3 days (p value=0.14) for ANC recovery and 16+11 days vs 14+9 days(p value=0.24) for platelet recovery respectively). The concentration of CD34 cells/kg of body weight was higher in the patients receiving apheresis products at concentrations less than 500 WBC/ml (5 x 10*6/kg vs 3.5 x 10*6 kg, p value = 0.028). For those patients who mobilize at less than optimal CD34 percentage of apheresis product, freezing at higher WBC concentrations allows for a reduction in volume and therefore a reduction in DMSO usage, fewer bags thus less freezer space used. Freezing at higher WBC concentrations does not appear to have an effect on days to ANC recovery to 500 cells/mm3 or platelet recovery to 20,000/mm3.

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SUPPRESSION OF EPSTEIN BARR VIRUS (EBV) RELEASE FROM IRRADIATED B LYMPHOBLASTOID CELL LINES (BLCL): SUPERIOR ACTIVITY OF GANCICLOVIR COMPARED TO ACYCLOVIR

Keever-Taylor, C.A.; Behn, B.; Konings, S.; Orentas, R.J.; Davies, B.; Margolius, D.A. Medical College of Wisconsin, Milwaukee, WI

BLCL generated by exposure of patient or donor B cells to a laboratory strain of EBV are commonly utilized in the preparation of T cell lines or clones used for post-transplant immunotherapy. Up to 5% of cells within the BLCL may contain infectious virus that could be released after stress such as that caused by irradiation. To reduce this risk, laboratories have included acyclovir (an inhibitor of DNA polymerase) at 100 mM in the BLCL cultures for ≥14 days prior to use. Validation studies were performed to determine the effectiveness of acyclovir in preventing EBV release through use of co-culture assays with cord blood mononuclear cells (CBMC) (ratio of 2:1 CBMC to BLCL). Both previously cryopreserved and freshly growing BLCL treated in the absence or presence of acyclovir were tested. The results showed that the irradiated BLCL (7,500 cGy) resulted in transformation of >85% of the CBMC co-cultures (N=104) regardless of acyclovir-treatment. Furthermore, doubling time of the BLCL was significantly reduced during acyclovir exposure. Additional CBMC co-culture experiments were performed using BLCL maintained for 14 days in ganciclovir at 0.5 and 1.0 μg/mL of culture. Here we found B cell transformation in 3/6 (50%) of cultures at 0.5 μg/mL and 2/6 (33%) of cultures at 1.0 μg/mL. CBMC co-cultures using BLCL grown in ganciclovir at 2.0 and 4.0 μg/mL have just been initiated. BLCL grew normally during the two-week treatment period at all doses of ganciclovir tested to date. While still preliminary, these results indicate that ganciclovir is more effective at preventing

release of infectious EBV from irradiated BLCL than acyclovir and is less inhibitory to B cell growth. However the optimal dose is yet to be determined.

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IN VIVO VERSUS EX VIVO B-LYMPHOCYTE PURGING OF PBPC FOR AUTOLOGOUS TRANSPLANTATION IN B-CELL NHL

Koç, O.N.; Meyerson, H.; Cooper, B.W.; Fox, R.M.; Gerson, S.L.; Laughlin, M.J.; Simic, A.; Lazarus, H.M. Departments of Medicine and Pathology, Ireland Cancer Center at CWRU and UHC, Cleveland, OH

We evaluated the safety and efficacy of B-lymphocyte purging of PBPCs in patients with B-cell NHL undergoing high dose chemotherapy. We randomized 12 patients to either receive i.v. Rituximab 375 mg/m^2 weekly x 3 just before mobilization (arm A n=5) or ex vivo purging of mobilized PBPCs using CD34 enrichment device CliniMACS (AmCell, CA) (arm B n=7). In arm B, 7 patients underwent a total of 10 CD34+ cell enrichment procedures. Mean CD34 yield was 62%±17 and the CD34 purity was 93±8 with average CD34+ cell enrichment of 250±198 fold. Total MNC infused (x 10^8/kg) was 10.3±6.2 for arm A and 0.05±0.02 for arm B. The number of CD3+ cells infused at the time of transplantation was significantly lower in ex vivo purged arm compared to the in vivo purged arm (0.01±0.01 vs. 37.4±17.8 x 10^6/kg). There was no significant difference in the number of CD34+ cells infused and there were no detectable B cells in either infusate. Following PBPC infusion, median time to neutrophils >500/µl was 9 (range 7-13) days for arm A and 10 (11-17) days for arm B, to platelets >20.000/µl 13 (8-17) days for arm A and 17 (13-23) days for arm B and to lymphocytes >500/µl 24 (9-130) days for arm A and 30 (25-142) days for arm B. CD3+ T-lymphocyte, CD19+ B-lymphocyte and immunoglobulin levels remained low in all patients for 3-6 months, although there was only 1 late infectious complication in arm A and 2 in arm B. Our preliminary data suggest that B-lymphocyte purging of PBPCs by either in vivo Rituximab therapy or ex vivo CD34+ cell enrichment using CliniMACS device is feasible without significant delay in myeloid engraftment. Effects of these manipulations on lymphoid engraftment and post transplant infectious complications are being investigated.

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INTERMEDIATE VERSUS STANDARD DOSE OF G-CSF FOR STEM CELL MOBILISATION IN HEALTHY DONORS FOR ALLOGENEIC TRANSPLANTATION

Kröger, N.; Renges, H.; Sonnenberg, S.; Krüger, W.; Gutensohn, K.; Dielschneider, T.; Cortes-Dericks, L.; Zander, A. University Hospital, Hamburg, Germany

We compared in a retrospective analysis two doses of recombinant human granulocyte stimulating factor (G-CSF) for stem cell mobilisation in 90 healthy donors for allogeneic stem cell transplantation. Group I (n=46) received 10 µg/kg G-CSF (Filgrastim) given as 5 µg/kg twice daily, and group II (n=44) received 16 µg/kg, given as 8 µg/kg twice daily with a 12 hour interval. The groups were well-balanced for age and body-weight. G-CSF application was performed on an out-patient basis, and leukapheresis was started in all donors on day 5. The most frequent side effects of G-CSF were bone pain grade I/II, headache grade I/II and fatigue grade I/II in both groups, whereas grade III of bone pain, headache and fatigue occurred in the 2 x 8 µg/kg group only. One serious non-fatal event with non-traumatic spleen rupture occurred in the 2 x 5 µg/kg group. The CD34+ cell count in the first apheresis of all donors was 5.1 x 106/kg donor weight (range, 1.5-19.3). The CD34+ cell harvest was higher in the 2 x 8 µg/kg group than in the 2 x 5 µg/kg group (7.1 x 106/kg vs. 4.9 x 106/kg; p=0.09). The target of collecting > 3.0 x 106 CD34+ cells/kg donor weight with one apheresis procedure was achieved in 95 % of group I and in 82 % of group II, respectively. The target of collecting > 5.0 x 106 CD34+ cells/kg in the first apheresis was achieved in 45 % and 61 %, respectively. Administering G-CSF at a dosage of 8 µg/kg twice daily leads to a higher CD34+ cell yield than a dosage of 2 x 5 µg/kg, but is associated with increased toxicity and higher cost.

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EFFECTS OF TRANSITIONAL STORAGE CONTAINERS ON RECOVERY OF TOTAL CELLS AND PROGENITOR CELLS AFTER THAWING OF BANKED UMBILICAL CORD BLOOD

Kurtzberg, J.; Waters-Pick, B.; Reese, M.; Avrutsky, S.; DeOliveira, D. Duke University Medical Center, Durham, NC

Umbilical cord blood, cryopreserved for transplantation, is traditionally stored submerged in liquid nitrogen (LN) (-190°C) until selection for transplantation. Three-5 weeks before a scheduled transplant, the donor unit is removed from LN, placed in a dry shipper (-150°C) and transported to the transplant center (TC), a process that takes 2-4 days. At the TC, the unit is either maintained in vapor phase (VP) or placed back under LN until the day of transplant (2-3 weeks later) when it is thawed and infused. To date, there has been no standardization of methods of storage after shipment. We investigated whether it would be better to resubmerge the unit under LN or to store in VP after removal from LN and shipment. Six cord blood units were collected, volume reduced and red blood cell depleted, divided into 2 equal aliquots and cryopreserved under LN in 10% DMSO in 2-compartment cryopreservation bags. Three weeks later, each unit was removed from LN, placed in a dry shipper for 4 days, and then either placed back under LN or stored in VP. At baseline, before cryopreservation, immediately upon removal from LN (before placement in the dry shipper, and 3 weeks later - after storage under LN or in VP, the units were thawed and assayed for cell counts, viabilities (trypan blue), CD34 cell content, and clonal progenitors. Recoveries of total cells and CD34 cells were superior in the units stored in VP as compared to LN. We suggest that this approach be adopted by transplant centers receiving and storing banked CBUs for transplantation therapy.

	% Total Cell Recovery	% CFU Recovery	% CD34 Cell Recovery
Immediate Thaw	93.1	48.5	98.9
Vapor Phase	78.9	38.8	89.4
Liquid Nitrogen	80.5	41.8	78.6

LYMPHOMA/MULTIPLE MYELOMA

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EVALUATION OF LYMPHOMAGENESIS IN THE HIGH-RISK, IMMUNOSUPPRESSED EBV-NAÏVE CHILD: ASSESSMENT OF AN EXQUISITLY SENSITIVE EBV ASSAY

Bonilla, P.J.; Bernard, M.V.; Dunn, S.P.; Krueger, L.J. Alfred I. duPont Hospital for Children, Wilmington, DE

B-cell posttransplant lymphoproliferative disorders (PTLD) encompass a broad spectrum differing from reactive plasmacytic hyperplasia to monomorphic B-cell lymphoma. Frank lymphoma is a major life-threatening complication of transplantation. The genesis of lymphoma is a multi-step process involving a series of incompletely defined environmental and genetic interactions. Two major risk factors are life-long immunosuppression and Epstein-Barr virus infection. Indeed, the ratio of PTLD in seronegative to sero-positive children is approximately 10:1. Using a robot-assisted 7900HT Sequence Detection System (Applied Biosystems Inc), a 20 µl PCR assay was developed priming the DNA polymerase gene. With TaqMan probes, this real-time analysis is precise for >5 magnitudes and detects 2.3 EBV genomes/assay. While this is sufficient to monitor the EBV-positive transplant child, it may not be optimal for the EBV-negative, highest risk patient. For this reason, we also targeted the internal repeat region. This semi-quantitative analysis highly increased sensitivity giving a 10-fold boost (avg. Ct = 21.6+0.2) over the clinical assay (avg. Ct = 25+0.1). To further increase detection sensitivity, the concentration of the DNA/assay was varied while the EBV concentration was held constant (see Table I.). Our current results suggest that this combined 30-45 fold increase in the

detection level of EBV can be still optimized using assiduous binding and better quenched fluorescent probes. Whether this level of sensitivity is an early warning system for primary infection or reactivation of donor latently infected cells remains for the future.

1R1 Region [EBV]	Total [DNA]	EBV Genomes Found	Efficiency	Fold Increase	Combined Increase
0.7 ng	126 ng	12, 785	1.225	1	12.25
0.7 ng	251 ng	10,716	1.027	2	20.54
0.7 ng	501 ng	9,389	0.900	4	36.00
0.7 ng	1001 ng	1,693	0.162	8	12.96

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SPLIT HIGH DOSE MELPHALAN WITH STEM CELL AND FILGRASTIM SUPPORT IN PATIENTS NOT ELIGIBLE FOR MYELOABLATIVE THERAPY

Conley, S.[1]; Reynolds, D.[1]; Moreb, J.[2]; Edwards, J.[3] 1. Halifax Medical Center, Daytona Beach, FL; 2. University of Florida, Gainesville, FL; 3. Walt Disney Memorial Cancer Institute, Orlando, FL

A common myeloablative chemotherapy regimen for Multiple Myeloma is Melphalan at 200 mg/m^2 given as a single infusion followed by an autologous stem cell transplant. Patients with significant co-morbidities are not eligible for myeloablative treatment which precludes entry into an transplant regimen. The only other treatment option has been aggressive conventional chemotherapy with cytokine support. Nonablative high dose Melphalan at 100 mg/m^2 with cytokine support has a prolonged pancytopenia period with greater than 25 days to recover granulocytes and platelets back to normal parameters. In order to provide the same dose intensity of drug with fewer complications we have enrolled patients in a pilot study to deliver Melphalan at 100 mg/m^2 followed by both stem cell and Filgrastim support. Study objectives are: to determine the feasibility of safely treating patients with this dose of Melphalan; to observe the toxicities of the treatment; and evaluate the response rate and time to progression. Patients able to tolerate a single cycle of treatment with full recovery were treated with a second cycle with stem cell and Filgrastim support. This approach ultimately delivers Melphalan at 200 mg/m^2 in a split dose regimen. To date 6 patients have been enrolled with the intent to treat when possible on an outpatient basis with hospital admission only for treatment related complications. The average day of stem cell engraftment to greater than 500 granulocytes/microliter is day +12 following stem cell infusion and initiation of Filgrastim. Patients were prophylaxed with antibacterial, antiviral, and antifungal oral therapy. To date one patient has required hospitalization for 3 days for dehydration and low grade fever. All patients have been able to proceed with the second cycle of therapy. Response to treatment and time to progression will be monitored and compared with conventional and high dose myeloablative therapy given in a single infusion.

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NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANT FOR MULTIPLE MYELOMA:A FEASIBILITY STUDY

Janakiraman, N.; Chamarthy, U.; Nath, R.; Vial, I.; Green, J.; Fortney, C.; Parikh, D. Henry Ford Hospital, Detroit, MI

Between May, 1999 and October 2001, eleven patients diagnosed with multiple myeloma underwent non-myeloablative allogeneic stem cell transplant (ASCT). Five males and 6 females with a median age of 54 years were enrolled on this study. Of the ten patients with multiple myeloma, 5 had kappa light chain, 3 had IgG kappa, and 1 each with IgA kappa and IgD lambda. One patient had extra-medullary plasmacytoma. The most common induction chemotherapy regimen was VAD. Three of 11 patients had relapsed after prior autologous BMT. The conditioning regimen included fludarabine, anti-thymocyte globulin and 140 mg/m^2 of melphalan. Cyclosporin and mycophenolate mofetil (Cellcept) were used for GVHD prophylaxis. Source of stem cells were HLA-matched siblings in 10 patients and unrelated donor in one. Median time to neutrophil engraftment (ANC > 500) was 12 days, with median platelet engraftment (> 20,000/mL) occurring at day 16. Donor engraftment was 100% by day 45 using VNTR technique. Nine of nine evaluable patients were in near CR on day 100. Three patients ultimately relapsed: 24 months, 7 months and 4 months, respectively. All relapses were treated with DLI. Grade III acute GVHD occurred in one patient and five others had Grade I (skin). Extensive chronic GVHD occurred in 5 of 8 evaluable patients. Limited chronic GVHD was documented in only one patient. Median follow-up is 8 months (range, 1 – 31 months). There were 3 deaths (ARDS/sepsis, progressive disease, and myocardial infarction). Conclusion: The moderate dose regimen used here with allogeneic stem cell transplant (ASCT) is associated with high response rate and is very well tolerated. Longer follow-up and quality of life studies are needed.

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HIGH INCIDENCE OF *CLOSTRIDIUM DIFFICILE* IN PATIENTS WITH MULTIPLE MYELOMA UNDERGOING AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

Restrepo, A.[1]; Schneider, D.L.[2]; Restrepo, M.I.[1]; Litofsky, I.D.[1]; Devore, P.E.[1]; Walsh, T.[1,2]; Gokmen, E.[1,2]; Ochoa, L.[1,2]; Callander, N.S.[1,2]; Freytes, C.O.[1,2] 1. University of Texas Health Science Center, San Antonio, TX; 2. South Texas Veterans Health Care System, San Antonio, TX

Introduction: Patients (pts) with Multiple Myeloma (MM) are predisposed to infections due to hypogammaglobulinemia and other immune defects. *Clostridium difficile* has been implicated in antibiotic-associated pseudomembranous colitis. The administration of broad-spectrum antibiotics and anti-neoplastic drugs lead to an intestinal environment that is conducive to the overgrowth of *C.difficile*. Previous studies report a low incidence of *C. difficile* associated diarrhea after Autologous Peripheral Blood Stem Cell Transplantation (APBSCT). **Purpose**: To determine the frequency of *C. difficile* infection during the first 30 days after APBSCT in MM patients. **Methods**: We retrospectively analyzed 83 consecutive patients with stage II and III Multiple myeloma following APBSCT at our institutions from February 1997 to September 2001. All patients with diarrhea underwent testing using the *C.difficile* stool toxin by immunoassay. Other causes of infectious diarrhea were excluded. **Results**: Of the 83 patients, 72 (87%) were men. Median age was 56 (range 41-78) and 75 (90%)patients had stage III MM at the time of APBSCT. The most frequent conditioning regimen utilized was melphalan in 55 pts (66%) and busulfan-cyclophosphamide in 12 pts (15%). Sixty-seven pts (81%) had fever after APBSCT. The median duration of neutropenia was 6 days (range 3–11). Patients received infection prophylaxis with acyclovir, fluoroquinolones and fluconazole. Patients with neutropenic fever were initially treated with a third generation cephalosporin or beta-lactam/lactamase antibiotics. *C. difficile* toxin was detected in 15 pts (18%) during the first 30 days after APBSCT. All patients received and responded to metronidazole therapy with resolution of diarrhea. **Conclusion** : *C. difficile* associated diarrhea is frequent in patients with MM during the first 30 days after APBSCT when compared to other studies. Multiple myeloma patients undergoing APBSCT with diarrhea should be evaluated for *C. difficile* infection. Better strategies should be developed to prevent infections in these individuals.

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ALLOGENEIC STEM CELL TRANSPLANTATION UTILIZING AN INTENSITY REDUCED REGIMEN WITH FLUDARABINE AND MELPHALAN RESULTS IN LOW TRANSPLANT RELATED MORTALITY AND LOW INCIDENCE OF RELAPSE IN MULTIPLE MYELOMA

Rodriguez, T.E.; Simpson, D.R.; Klingemann, H.G. Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL

High Dose chemotherapy and allogeneic stem cell transplantation is capable of inducing long term survival in patients with Multiple Myeloma. Nevertheless, the high transplant related mortality of approximately 25-50% observed in this population limits the benefits of this treatment modality. We report our experience in 17 patients with advanced Multiple Myeloma who underwent

allogeneic stem cell transplantation with an intensity reduced regimen consisting of Fludarabine 30 mg/m2 x 3 (D-5 to -3) and Melphalan 80 mg/m2 x 2 (D-2, -1). All patients received G-CSF (10mg/kg/day x 4) mobilized, 6/6 HLA-matched sibling donor stem cells. Graft Versus Host Disease prophylaxis consisted of Cyclosporine and Methotrexate. The median age was 53 years (range 39-61). Patients received a median stem cell dose infusion of 3.74 x 10^6 CD34+ cells/kg (range 2.3-7.55). **Results:** The median time for patients to achieve an absolute neutrophil count = 0.5 x 10^9 /L was 13 days. No graft rejection was observed. Of 12 evaluable patients, 11 were ≥ 96% donor T-cell chimeras at day +100. One patient developed mixed chimerism (93% donor T-cell) for which quick tapering of Cyclosporine was initiated. Four patients have died since the initiation of this study. One (5%) patient died before day +100 from a contaminated platelet transfusion. The other three patients died from disease progression. With a median follow up of 15 months, the Kaplan Meier probability of overall survival is 87% and the probability of progression free survival is 76%. **Conclusion:** We conclude that an intensity reduced regimen consisting of Fludarabine and Melphalan is a suitable preparative regimen for allogeneic transplantation in patients with advanced Multiple Myeloma, resulting in adequate engraftment, low incidence of transplant related mortality, and low incidence of relapse.

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ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION FOR HIGH-RISK NON-HODGKIN'S LYMPHOMA

Seropian, S.; Bahceci, E.; Cooper, D. Yale University, New Haven, CT

The use of PBSC for allogeneic transplantation has been associated with improved outcome compared to bone marrow in high risk patients. 28 consecutive NHL patients with high risk features for regimen related toxicity (RRT) and disease recurrence were enrolled on clinical protocols utilizing PBSC with a traditional ablative or modified conditioning regimen. 21 patients had intermediate/high grade histology, 7 had low grade. Risk factors included age >50 (n=16), Refractory disease (n=15), failed autologous transplant (n=11), abnormal organ function (n=2). Median age of patients receiving ablative or modified conditioning was 47 and 57 years respectively. Ablative regimens included TBI/CY (n=8), BEAM (n=7), Bu/Cy (n=1), TBI/TT/Flu (n=1). Eleven patients received a modified regimen including Fludarabine, (IV)Busulfan and ATG. Tacrolimus and low dose methotrexate (5mg/m2 on days +1,+3,+6) were used for GVHD prophylaxis. PBSC were mobilized from normal donors following Filgrastim 10mcg/kg daily or 6mcg/kg BID for 3-4 days. A median of 5.09 x 10e6 CD34+ cells were infused. Neutrophil and platelet engraftment both occurred at a median of 12 days post transplant. Three patients died prior to day 100 of RRT (2) and GVHD (1). Grade II-IV AGVHD occurred in 9/27 and Grade III-IV AGVHD occurred in 2/27 evaluable patients. Extensive CGVHD occurred in 21/24 evaluable patients. In 7 patients GVHD appeared to be the direct result of withdrawal of immunosuppression +/- DLI to treat persistent or recurrent disease. With a median follow up of 796 days, disease free and overall survival are 57% and 69%. "Current disease free survival" is 68% as 3/10 patients with recurrent/persistent disease post transplant responded to additional therapy including withdrawal of immunosuppression +/- DLI suggestive of a graft versus lymphoma effect. These results suggest that the use of PBSC and risk-adjusted conditioning is associated with improved outcome in this high-risk population.

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LEVELS OF DETECTION OF MYELOMA CELLS BY MOLECULAR METHODS: COMPARISON BETWEEN NESTED PCR AND RQ-PCR WITH THE TAQ-MAN CYCLER

Togel, F.E.; Kröger, N.; Fehse, B.; Zander, A.R. University-Hospital Eppendorf, Hamburg, Germany

Multiple myeloma is a malignant disease characterized by infiltration of bone marrow sites with plasma cells.Treatment with high dose therapy results in a high rate of clinical remissions, but almost all patients ultimately relapse. Clinical staging and detection of relapse is limited in sensitivity. Therefore, we established molecular methods using the highly clone-specific CDR regions of the immunoglobulin VH locus for sensitive and specific detection of residual myeloma cells. Methods: VDJ rearrangements were identified using a set of VH-primers and a JH primer. Clone-specific mutations in the CDR regions were identifid by comparison with germline sequences. Primers were designed using primer express software. With the nested PCR approach first round amplification with the VH family primer and the JH primer was done followed by second round amplification with myeloma-specific primers. The specific band of exspected size was visualized on agarose. Taq-Man PCR was performed using a myeloma-specific forward primer in combination with a JH-consensus Taq-Man probe and reverse primer. Taq-Man PCR results were analysed with the applied-biosystems software. Results: Sensitivity was tested using dilutions of myeloma cell lines into normal mononuclear cells. Nested PCR had a sensitivity of 10-6 and Taq-Man PCR 10-5. Specifity was determined by testing different cell lines and patients . With accurate primer design high annealing temperature no unspecific positive results were observed. These results were confirmed by follow up of three patients after dosis reduced conditioning and allogeneic transplant. One patient in clinical remission is still positive with nested pcr, but tumor-load as measured by Taq-Man PCR is lower 0,001% myeloma cells. Conclusion: Molecular methods are a very sensitive and specific tool for follow up of myeloma patients after allogeneic bone marrow transplantation. By using the quantitative approach it is possible to see kinetics of bone marrow tumor-load which can be used to guide therapeutic decisions like DLI.

SOLID TUMORS

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HER-2 OVEREXEPRESSION AS PROGNOSTIC FACTOR IN METASTATIC BREAST CANCER (MBC) PATIENTS TREATED WITH HIGH-DOSE CHEMOTHERAPY (HDC)

Guarneri, V.[1]; Bengala, C.[1]; Orlandini, C.[1]; Pazzagli, I.[1]; Landucci, E.[1]; Cecchetti, D.[2]; Campani, D.[2]; Conte, P.[1] 1. Division of Medical Oncology S. Chiara University Hospital,, Pisa, Italy; 2. Division of Pathology, S Chiara University Hospital, Pisa, Italy

In breast cancer HER-2 overexpression is associated with worse prognosis;preliminary data suggest that HDC might overcome the negative prognostic impact of this factor. To explore this possibility we have analyzed 32 MBC patients treated with HDC after induction chemotherapy. 22 pts received a single course of HD thiotepa+melphalan; 10 pts received also a second course of HD idarubicin. HER-2 overexpression was determined by IHC using TAB-250 and Herceptest.At study entry patients characteristics were as follows: median age 48 yrs (range 28-57);hormone receptor negative in 46% of pts; median number of metastatic sites 3(range 1-5); HER-2 overexpression in 41% of pts. Before HDC 19% of the pts were in complete remission (CR), 69% in partial remission (PR) and 12% had stable disease (SD).After HDC 47% of the pts were in CR (conversion rate 34,3%) and 53% in PR.Median progression free survival (PFS) and overall (OS) were 21.4 months (mo) (95% CI 16.4-26.4) and 48.5 mo (95% CI 28.4-68.6) respectively.Median PFS of the pts with p-185> and < 70% were 14.3 mo (95% CI 10-18.5) and 19 mo (95% CI 15-23) respectively (p=0.05). Median OS were 27.63 mo (95% CI 16.4-38.8) and 50.3 mo (95% CI 42.6-58.09) for the pts with high and low HER-2 positivity respectively (p=0.23). According to Herceptest, median PFS of patients with score 3+ and 0-2+ was 11.8 mo (95% CI 7.3-16.4) and 19 mo (95% CI 14.25-23.7) respectively (p: 0.01). Median OS was 19.4 mo (95% CI 5.3-33.4) and 50.3 mo (95% CI 35-65.6) in patients with score 3+ and 0-2+ respectively (p: 0.04).Our data shows an increased incidence of Her -2 overexpressione; moreover Her 2 overexpression is related to worse PFS and OS, inspite of HDC.

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HIGH-DOSE CHEMOTHERAPY (HDC) WITH BOLUS STAMP V AND PERIPHERAL BLOOD STEM CELL TRANSPLANT (PBSCT) FOR EARLY STAGE HIGH-RISK PRIMARY BREAST CANCER (HRPBC) IN A COMMUNITY-BASED ONCOLOGY NETWORK

Williams, S.; Cuasay, L.; Mandanas, R.; Quiett, K.; McGuirk, J.; Rifkin, R.; Beveridge, R. US Oncology, Houston, TX

The role of HDC with PBSCT in breast cancer remains controversial. HRPBC has a high recurrence rate after standard adjuvant therapy. US Oncology's network of community-based stem cell transplant programs (21 centers in 16 states) used HDC and transplanted 234 HRPBC patients between August 1996 and June 2000. All patients were treated with bolus STAMP V consisting of Cyclophosphamide 6,000 mg/m^2, Thiotepa 500 mg/m^2, and Carboplatin 800 mg/m^2 divided equally over 3 days, followed by stem cell reinfusion. All patients, except one, were female. Median age was 47.5 years (range: 27-65). At diagnosis, 179 (76.5%) were stage II and 55 (23.5%) were stage III; 62.4% were ER or PR positive. Hematopoietic growth factors were used to accelerate engraftment. Median time to ANC ≥500 cells/μL was 10 days; median time to platelet count ≥20,000 cells/μL was 12 days. Eighty-seven (37.2%) required hospitalization within 28 days post-transplant. All deaths were due to disease progression or relapse; two (0.9%) occurred within 100 days. With median follow-up of 23.6 months (range: 0.5-52), 1- and 3-year OS were 95.6% and 85.6%, while 1- and 3-year DFS were 81.5% and 60.8%. There were no significant differences in OS and DFS according to stage and positive lymph nodes (<10 vs. ≥10). (Table) HDC with PBSCT can be safely administered to patients with early stage HRPBC in the community setting. Results of completed randomized clinical trials are eagerly awaited.

	1-yr OS	3-yr OS	1-yr DFS	3-yr DFS
≤45 yrs old	94.6	85.7	76.4	53.5
>45 yrs old	96.3	85.5	85.1	65.5
		n.s		P=0.015
ER or PR positive	97.0	90.2	85.4	65.5
ER and PR negative	92.5	75.1	72.4	54.1
		P=0.002		P=0.009

STEM CELL BIOLOGY

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CYCLOSPORINE (CSA) MEDIATED INHIBITION OF P-GLYCOPROTEIN (P-GP) ACTIVITY IN HEMATOPOIETIC PROGENITOR CELL SUBSETS: IMPLICATIONS FOR DRUG INTERACTIONS IN THE POST TRANSPLANT PERIOD

Donnenberg, V.S.; Griffin, D.L.; Yeager, A.M.; Donnenberg, A.D. University of Pittsburgh Cancer Institute, Pittsburgh, PA

INTRODUCTION: Hematopoietic engraftment following stem cell transplantation depends on the proliferation and differentiation of hematopoietic progenitor cells. Even after engraftment, transient depression of peripheral counts is common. Progenitor cells protect themselves from xenobiotics by multiple drug resistance pumps including ABCG2 and P-gp in the primitive side population and P-gp in committed hematopoietic progenitor cells. Allogeneic stem cell transplant recipients are exposed to a variety of therapeutic agents in the immediate post transplant period, many of which are substrates for and/or inhibitors of P-gp. In particular, cyclosporine (CsA) inhibits P-gp in the micromolar range. METHODS/RESULTS: Since P-gp inhibition could render progenitor cells more susceptible to toxic insults and unanticipated drug interactions, we evaluated the effects of CsA on CD34+ peripheral blood progenitor cells (PBPC), subsetted on into CD38+ (more differentiated) and CD38- (less differentiated) cells. We used a rhodamine 123 (R123) dye efflux assay to measure basal and substrate induced P-gp activity in the absence and presence of CsA (5 microM). Neither CD34 subset expressed significant basal P-gp activity, as measured by R123 efflux in short term (15') culture. In the absence of CsA, both subsets evidenced strong and homogenous substrate-induced activity (measured from 15-180 minutes in culture). Addition of CsA (5 microM) only partially inhibited R123 efflux in both subsets. In contrast, verapamil (50 microM), a model P-gp inhibitor, blocked dye efflux only in CD38- CD34+ cells. CONCLUSIONS: The absence of basal activity is consistent with the absence of substrate-induced P-gp activation in vivo. Partial blockade by CsA may indicate a CsA resistant pump or an insufficient CsA dose. Blockade of primitive, but not differentiated progenitors by verapamil may indicate the activity of a pump distinct from P-gp and ABCG2 in these cells.

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PLATELET-DERIVED MICROPARTICLES BIND TO HEMATOPOIETIC STEM/PROGENITOR CELLS AND ENHANCE THEIR ENGRAFTMENT AFTER TRANSPLANTATION

Janowska, A.[1]; Majka, M.[2]; Ratajczak, M.Z.[2] 1. University of Alberta, Edmonton, AB, Canada; 2. University of Louisville, Louisville, KY

Since human CD34+ cells as well as murine Sca-1+ hematopoietic stem/progenitor cells (HSPC) express platelet-activating sialomucin P-selectin (CD162) and integrin Mac-1 (CD11b/CD18) antigen we inferred that these cells may interact with platelets. As a result of this interaction, microparticles derived from platelets (PMPs) could transfer many platelet antigens (CD41, CD61, CD62, CXCR4, PAR-1) to the surface of HSPC. To determine the biological significance of the presence of PMPs on human CD34+ and murine Sca-1+ cells we initially compared their expression on mobilized peripheral blood (mPB)- as well as non-mobilized PB- and bone marrow (BM)-derived CD34+ cells and then studied the effects of PMPs on i) proliferation of CD34+ and Sca-1+ cells and ii) adhesion of HSPC to endothelium and immobilized SDF-1. Finally, we examined the hematopoietic reconstitution of lethally-irradiated mice transplanted with BM mononuclear cells covered or not covered with PMPs. We found that PMPs (i) are more numerous on mPB than BM CD34+ cells, (ii) do not affect the clonogenicity of human and murine HSPC, and (iii) increase adhesion of these cells to endothelium and immobilized SDF-1. Moreover, murine BM cells that we covered with PMPs engrafted in lethally-irradiated mice significantly faster than those not covered, indicating that PMPs play an important role in the homing of HSPC. This could explain why in a clinical setting human mPB HSPC (densely covered with PMPs) engraft more rapidly compared to BM HSPC, with fewer. Our findings indicate a new role for PMPs in stem cell transplantation and may have clinical implications for optimizing transplantation.

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EXAMINATION OF THE NECESSITY FOR SERIAL BLOOD CULTURES IN FEBRILE STEM CELL TRANSPLANTATION PATIENTS

Liesveld, J.L.; Hall, D.; Wedow, L.; MacDonald, G.; Hardy, D. University of Rochester Med.Ctr./SMH, Rochester, NY

Fever in stem cell transplant (SCT) patients prompts empiric antibiotic therapy and obtaining blood cultures to monitor for presence of bacterial infections. The University of Rochester SCT unit has a policy that blood cultures are obtained at least once every 24 hours while the patient remains febrile and at times when a febrile patient's clinical condition changes. Given the low overall frequency of positive blood cultures in our patient populations (0.084), we examined retrospectively whether changing culture frequency to every 48 hours might result in cost savings without compromise of patient safety. The study sample consisted of all blood cultures obtained on the transplant unit in patients undergoing myeloablative conditioning from January to October, 2000. Episodes that had only one initial blood culture and no subsequent draws were excluded. 124 cultured febrile episodes occurred with an average length of 4 days. A binary probity analysis revealed that the result of the initial culture was a good predictor of the result of the second culture at 24 hours (p-value .0087 and McFadden R-squared value 0.1017). The probability of the second draw being positive when the first draw was negative was only

4.5%. In matched unrelated donor transplants, this probability rose to 10%. The predictability of the first draw on the third (48 hours) result was not accurate. The predictive value of the first blood culture result, therefore, suggests safety of waiting 48 hours for a second blood culture draw in febrile autologous and matched sibling allogeneic transplant patients begun on broad spectrum antibiotics empirically. Since the cost of each negative blood culture at our institution is $65.75 (raw materials, laboratory costs, and nursing times), the policy to perform blood cultures every 48 versus every 24 hours would result in a 50% reduction in the blood culture budget.

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IDENTIFICATION OF A CANDIDATE HUMAN NEUROHEMATOPOIETIC STEM-CELL POPULATION

Shih, C.; Weng, Y.; Mamelak, A.; LeBon, T.; Forman, S.J. City of Hope National Medical Center, Duarte, CA

It was recently reported that transplantation of clonally derived murine neural stem cells (NSCs) into sublethally irradiated allogeneic hosts lead to a donor-derived hematopoietic reconstitution. The confirmation of the existence of a common neurohematopoietic stem cell in human brain will have a significant impact in stem cell research and in clinical transplantation. In this study, we have investigated if human NSCs possess in vivo hematopoietic potential in SCID-hu mice. Our results demonstrate that human fetal brain tissues contain separate but overlapping EGF- and FGF-2-responsive NSCs. These human NSCs express characteristic neural stem/progenitor cell markers including nestin, and receptors for EGF and FGF-2. These human NSCs can be maintained and expanded in vitro for many passages and still retain their self-proliferative and multilineage potential for neurons, astrocytes, and oligodendrocytes. Our first approach to determine the hematopoietic potential of human NSCs was to culture the human NSCs in a murine stromal co-culture system which has been previously developed in our laboratory and supports ex vivo human hematopoietic stem cell expansion. Results from in vitro co-cultures did not show detectable human hematopoietic cells. These results suggest that this stromal co-culture system is not sufficient to support differentiation of human NSCs into hematopoietic cells in vitro. The SCID-hu mouse model was then utilized to determine if a human bone marrow (BM) microenvironment is required for hematopoietic differentiation of human NSCs. One million human NSCs were injected directly into each human graft, including thymus and bone fragment, in SCID-hu mice, and NSCs-derived hematopoietic cells (HLA-MA2.1-positive) in those injected human grafts were analyzed 4 months after NSC injection. Our results demonstrate that cultured human NSCs do possess in vivo hematopoietic potential, and that differentiation of cultured human NSCs into hematopoietic lineages depends on the presence of an intact human BM microenvironment.

SUPPORTIVE CARE

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AMBISOME® PROPHYLAXIS IN PATIENTS UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT)

Cairo, M.S.; DiNatale, J.; Harrison, L.; Wolownik, K.; Bessmertny, O.; Del Toro, G.; Bradley, B.; Yamashiro, D.; Garvin, J. Children's Hospital of New York Presbyterian, Columbia University, New York, NY

Walsh et al (NEJM 1999; 340: 764-71) reported a randomized, multi-center trial comparing liposomal amphotericin B (AmBisome®) (AmB) with amphoB in patients that developed fever and neutropenia (45% BMT recipients) but not given prophylactically, and demonstrated significantly fewer breakthrough fungal infections with AmB vs. amphoB (3.2 vs. 7.8%)($p<0.009$). We initiated a pilot study to determine the safety and efficacy of AmB given prophylactically to AlloSCT recipients. Twelve AlloSCT patients were given AmB prophylactically (3 mg/kg) IV once a day, day 0 to day +100. Median age of the recipients was 11.5 years (range 2-21 years), 5 F and 7 M; 3 ALL (2 CR2, 1 CR3), 2 HD NED, 1 AA, 1 SS, 1 relapsed AML, 1 refractory Hodgkin's, 1 lymphoblastic lymphoma, 1 CML -CP, and 1 WAS. Donor types were UCB (2:5/6; 5:4/6), 3 6/6 HLA matched related PBSC, and 2 BM. All patients received FK506/MMF GVHD prophylaxis. Only 1/12 patients required premedication with Tylenol® and Benedry®. AmB was well tolerated with 2 pts experiencing grade 3 hypokalemia, 2 with grade 3 creatinine and 1 with grade 3 hypotension. There have been no (0%) documented emergent systemic fungal infections. 3/12 patients died (1 grade IV GVHD, 1 PD, 1 respiratory failure 2° to ARDS) and no evidence of fungal infections on autopsy. These preliminary results suggest that AmB may be given safely prophylactically and may be effective in the prevention of emergent systemic fungal infections in related and unrelated AlloSCT recipients. Larger studies are required to determine the overall safety of this approach and its potential efficacy compared to other approaches.

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USE OF A SUPPORTIVE CARE TEAM FOR SCREENING AND PREEMPTIVE INTERVENTION: PRETREATMENT LEVELS OF DISTRESS, FATIGUE, PAIN, NUTRITIONAL RISK, AND SEXUAL CONCERNS AMONG STEM CELL TRANSPLANT PATIENTS

Coleman, E.; Griffith, K.; Sherman, A.C.; Cromer, J.; Simonton, S.; Latif, U.; Hine, J.; Farley, H.; Garcia, R.; Knight, M.; Krishnan, S.; Anaissie, E.J. University of Arkansas for Medical Sciences, Little Rock, AR

Stem cell transplant (SCT) patients may be burdened by extensive physical symptoms and quality-of-life impairments. These difficulties may be evident even prior to aggressive treatment; often they are overlooked or are managed episodically. Recently we pilot-tested an interdisciplinary supportive care program designed to facilitate early screening and preemptive treatment. This pilot program was developed to identify patients at risk during their initial work-up for SCT, to reduce subsequent complications. 61 patients were assessed during their initial clinic evaluation. Average age was 57.0; 63.9% were male, and 91.8% were white. Most patients had multiple myeloma (85.3%). Average time since diagnosis was 7.4 months, and extent of prior treatment varied widely. Clinical interviews were conducted by a nurse practitioner, supplemented by validated measures of distress (Hospital Anxiety and Depression Scale), fatigue (POMS-Fatigue), pain (Brief Pain Inventory), nutritional risk (PG-SGA), sexual difficulties (rating scales), and quality-of-life (SF-12). The prevalence of symptoms was high across multiple spheres of functioning. The majority (58.1%) scored substantially below national norms for physical dimensions of quality-of-life (SF-12 PCS). Nutritional deficits were evident for 59.7%. Forty-seven percent exceeded cut-offs for fatigue. Thirty-one percent of patients reported elevated levels of distress; 27.9% scored within the "probable case" range for anxiety and as did 24.6% for depression. Average pain intensity was moderate or greater for 35.9% of patients; it was severe for 13.2%. Similar percentages reported that day-to-day life was at least moderately (36.4%) or severely (18.2%) impaired due to pain. Difficulties with body image and sexual functioning were noted by 35.6%. Findings suggest that a substantial proportion of patients would benefit from supportive care screening early in the course of treatment, prior to beginning conditioning regimens and transplant. Early, systematic screening for physical and emotional symptoms appears to be feasible and may contribute to improved care.

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ORAL GLUTAMINE TO IMPROVE NUTRITION AND REDUCE GASTROINTESTINAL TOXICITY IN STEM CELL TRANSPLANTATION

Conley, S.; Carbley, R.; Reynolds, D.; Alexander, J.; Alexander, C.; Sorathia, A.; Luwisch, E. Halifax Medical Center, Daytona Beach, FL

The maxi-ICE induction transplant regimen with Ifosfamide, Carboplatin and Etoposide induces severe documented gas-

trointestinal toxicity requiring total parenteral nutrition. From 1996 - 1999 ten patients who received maxi-ICE were enrolled in an institutional study to receive oral glutamine at 0.5 mg/kg/day in divided doses not to exceed a total dose of 40 mg/day beginning the day of high dose chemotherapy and continued until oral intake could not be accomplished due to mucositis. Outcomes were initially compared to published retrospective data describing the toxicities observed with the same maxi-ICE regimen as reported by the Moffitt transplant group in Tampa. In comparing the maximum recorded toxicity scores for mucositis and enteritis the Halifax group appeared to score higher than the Moffitt data base. However because of the differences in subjective scoring between two transplant teams using the WHO scales this was judged to be an unreliable comparison. Using the Halifax data alone the number of continuous days of mucositis was consistently decreased as the maximum cumulative recorded doses of glutamine taken increased. In addition the days of TPN required directly correlated with the total cumulative dose of oral glutamine taken with statistical significance using linear regression (P = 0.046). Previous published reports of oral glutamine to reduce GI toxicity in the transplant population have been conflicting. This may be due to a combination of patients treated with different regimens many of which induce only mild mucositis. Other glutamine studies have also employed lesser doses of oral glutamine compared to that used in the study reported here. The only statistical findings in the current study relate to more benefit as the amount of oral glutamine is increased. However this appears to be a very cost effective supportive care method to reduce morbidity in regimens that induce significant gastrointestinal toxicity.

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COMPARISON OF TREATMENT EFFECTS BETWEEN BETADINE/NYSTATIN AND GM-CSF ORAL GARGLINGS AMONG PATIENTS WITH CHEMOTHERAPY INDUCED STOMATITIS

Hong, J.; Kwon, I.; Huh, S.; Jung, M.; Park, C. Samsung Medical Center, Seoul, South Korea

- purpose : This study was conducted to compare treatment effects between betadine/nystatin and GM-CSF oral garglings among patients with chemotherapy induced stomatitis, grade 2 or higher. - method : From May 2000 to September 2001, 30 subjects with chemotherapy induced stomatitis, grade 2 or higher by Nicolatou method, among BMT, hematologic malignancy and other solid cancer patients were recruited. 19 subjects were treated by GM-CSF solution (400ug GM-CSF + 40ml normal saline, 4 times a day) and 11 subjects were treated by conventional betadine/nystatin solution. All subjects were allocated conveniently. - results : There were no significant differences of age, sex, disease conditions, treatment types, smoking habit, oral hygiene and ECOG score between two groups. The duration from starting date of treatment to fully recovered date were not different between two groups(GM-CSF group was 8.21days and betadine/nystatin group was 9.7days). But in 10days after treatment, GM-CSF group showed better effect curve than betadine/nystatin group by using survival data analysis, and in the aspect of effecting point, GM-CSF group revealed faster than betadine/nystatin group, by 6 days grossly, and by 4 days functionally. The mean numbers of ANC at 2nd day from treatment were 341/ul and 502/ul, and at 6th day, 1,350/ul and 1,342/ul, of each GM-CSF group and betadine/nystatin group, but no significant difference was found by using mixed model analysis. - conclusion : Although there were no enough statistically significant differences between GM-CSF and betadine/nystatin groups, GM-CSF treatment could be strongly recommended as a treatment of choice of chemotherapy induced stomatitis, because GM-CSF treatment showed faster effect than betadine/nystatin treatment.

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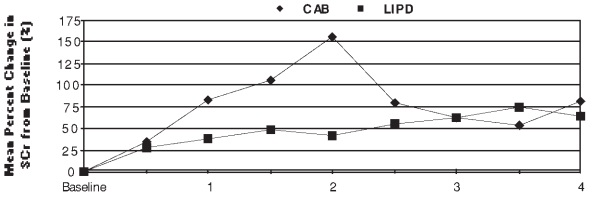
A MULTICENTER, RETROSPECTIVE STUDY OF AMPHOTERICIN B-INDUCED NEPHROTOXICITY IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC PROGENITOR CELL TRANSPLANT (HPCT) RECIPIENTS WITH INVASIVE FUNGAL INFECTIONS (IFI)

Kletzel, M.[1]; Chan, K.[2]; Kapoor, N.[3]; Seibel, N.L.[4]; Sandler, E.S.[5]; Fleck, P.R.[6]; Blatt, J.[7]; Bunin, N.[8]; Goldman, F.D.[9] 1. Children's Memorial Medical Center, Chicago, IL; 2. University of Texas M.D. Anderson Cancer Center, Houston, TX; 3. Children's Hospital Los Angeles, Los Angeles, CA; 4. Children's National Medical Center, Washington, DC; 5. Nemours Children's Clinic, Jacksonville, FL; 6. Cincinnati Transplant Institute, Cincinnati, OH; 7. University of North Carolina at Chapel Hill, Chapel Hill, NC; 8. Children's Hospital of Philadelphia, Philadelphia, PA; 9. University of Iowa Hospitals & Clinics, Iowa City, IA

Pediatric allo-HPCT recipients are at high risk for IFI, and Amphotericin B (AMB) is the gold standard of therapy. Limited data is available regarding patterns of AMB-induced nephrotoxicity in these patients. A multicenter, retrospective chart review of 58 pediatric HPCT recipients treated with AMB between 1995-2000 for proven or probable IFI was conducted in 8 centers. Twenty-four patients were initiated on CAB (mean dose 0.71±0.34 mg/kg/day) and 34 were initiated on LIPID (mean dose 4.0±2.0 mg/kg/day). There were no significant differences in baseline demographics between the two treatment groups. Following initiation, 67% of CAB patients required conversion to a LIPID formulation, while 18% of patients initiated on LIPID were converted to another LIPID (p=0.001). Nephorotoxicity accounted for 81% of CAB patient conversions. The figure shows the mean percent change in SCr from baseline over time in both initial treatment groups, which was significantly less in children who received LIPID in the first two weeks of therapy (p<0.05). SCr changes from weeks 3-4 were not significant because most remaining patients had switched to LIPID* (median 3.5 days). Only 3/24 (13%) patients started on CAB remained on initial therapy at week 4, compared to 25/34 (74%) patients started on LIPID. Insert figure here Conclusion: Initiating patients on CAB therapy results in the majority being switched to a LIPID formulation due to nephrotoxicity. Treatment may be better tolerated and administered for a longer duration if patients are initiated on LIPID since their SCr changes over time do not increase as rapidly as patients initiated on CAB.



	Week				
	Baseline	1	2	3	4
CAB/Lipid*	24/0	8/16	7/16	4/15	3/11
Lipid	34	34	32	28	25

* Shows disposition of patients switching from CAB to Lipid

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SURVEILLANCE BLOOD CULTURES PERMIT EARLY DETECTION OF POTENTIALLY SERIOUS BLOODSTREAM INFECTIONS IN ASYMPTOMATIC OUTPATIENTS WITH GRAFT-VERSUS-HOST DISEASE

Langston, A.A.; Teagarden, D.; Mossavi-Sai, S.; Wright, L.; Redei, I.; Lonial, S.; Waller, E.K.; Nolte, F.S.; Somani, J. Emory University School of Medicine, Atlanta, GA

The antipyretic effect of corticosteroids may confound detection of infections, which are the leading cause of mortality among pts with graft-versus-host disease (GVHD). At our institution, we obtain regular surveillance blood cultures on all pts receiving corticosteroid therapy for GVHD. We examined the yield and microbiology of outpatient surveillance cultures by retrospective study of 33 consecutive pts transplanted between 1/99 and 4/01 who developed acute (grades II-IV) and/or chronic extensive GVHD after matched sibling (n=23),

unrelated (n=8), or mismatched family donor allografts (n=2). GVHD sites included skin (22 pts), GI (20 pts), liver (1 pt), and polyserositis (2 pts). Surveillance cultures, drawn from an indwelling catheter, began at a median of 49 days post-transplant. Cultures obtained from febrile (>38C) pts were excluded. Coagulase negative staphylococcus, diphtheroids (except Corynebacterium JK), and micrococcus were considered contaminants unless isolated from consecutive cultures. Other organisms were considered significant if isolated from any blood culture. Using this definition, 32 separate bloodstream infection episodes were identified from cultures drawn at 605 clinic visits (5% yield); this represented 53 (4.6%) of 1149 individual cultures. Eight episodes (25%) were polymicrobial. Isolates included 20 gram positive bacteria, 12 enteric and 6 environmental gram negatives, and 1 yeast (Candida albicans). Positive cultures occurred in 15 of the 33 pts; mean prednisone dose was 50 mg/day (range 16-120) at the time of positive cultures. In univariate analyses, positive cultures were associated with longer duration of prednisone therapy (p=0.01), and secondary therapy for refractory GVHD (p=0.04). Presence of skin GVHD was associated with a reduced likelihood of positive cultures in univariate (p=0.02) and multivariate analyses (p=0.046). All episodes were successfully treated with systemic antibiotics. These data indicate that occult bloodstream infections occur with significant frequency in GVHD pts receiving corticosteroid therapy, and support the practice of surveillance blood cultures in this population.

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COMBINATION GANCICLOVIR AND FOSCARNET TREATMENT OF CYTOMEGALOVIRUS (CMV) AFTER ALLOGENEIC TRANSPLANT FOR PATIENTS FAILING SINGLE AGENT THERAPY

Morris, J.D.[1]; Landers, R.[1]; Saccente, C.S.[1]; Arzoumanian, V.[2]; Morris, C.L.[2] 1. Arkansas Children's Hospital, Little Rock, AR; 2. University of Arkansas for Medical Sciences, Little Rock, AR

We treated 4 patients with hematological malignancies who failed single agent therapy for CMV following allogeneic stem cell transplant, 2 with reactivation and 2 with CMV colitis, with combination ganciclovir and foscarnet therapy. Onset of CMV reactivation occurred on day 40 and 44 in 2 patients and CMV colitis was diagnosed on day 91 and 100 in 2 patients. Three patients had graft versus host disease (GVHD) at the time of CMV reactivation (n=1) with skin GVHD or CMV colitis (n=2) with gut GVHD, and 1 patient had no GVHD. Patients were initially treated with standard induction doses of ganciclovir (5mg/kg i.v. Q12H, n=3) or foscarnet (100mg/kg i.v. Q12H, n=1) for 9 to 21 days. Combination therapy was initiated when treatment failure was documented by rising CMV peripheral blood antigen level (n=1) after 9 days, persistent fever after 13 days of ganciclovir induction therapy (n=1), or by persistence of symptoms of colitis and CMV inclusions on biopsy of colonic mucosa after 17 to 49 days of treatment (n=2). All 4 patients were symptomatic with CMV-induced fever (n=2) or colitis (n=2) at the time combination therapy was initiated. Patients cleared CMV antigen (n=1), fever (n=1), or colitis (1 biopsy proven and 1 by symptoms) within 5 to 20 days of combination therapy. No significant hematological or renal dysfunction was seen with combination therapy. Combination therapy with ganciclovir and foscarnet is a promising treatment for patients failing single agent therapy and warrants a prospective trial.

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EFFECTS OF HIGH DOSE CHEMOTHERAPY ON SYSTOLIC CARDIAC FUNCTION AS MEASURED BY LEFT VENTRICULAR EJECTION FRACTION (LVEF)

Nayak, S.; Shikhman, S.; Garner, P.; Dorr, S.; Akhtar, A.; Momin, F. Oakwood Hospital, Dearborn, MI

Purpose: To study the effects of high dose chemotherapy (HDCT) on LVEF in patients undergoing auto and allo stem cell transpalntation. Methods. Our protocols require assessment of LVEF pre HDCT and 100 days post HDCT. Pre HDCT LVEF of < 40% excludes patients from HDCT protocols. Cardiac function of 42 autologous and 11 allograft recipents was studied pre and 100 days post HDCT. The median age was 53 yrs (27 - 72 yr). Male/Female ratio was 19/34. Standard HDCT regimens included STAMP V, BU/CY2, BAC, CVB, Melphalan 200mg/m2. Sixteen had breast cancer, 35 had hematological malignancies and 2 had ovarian cancer. Cardiac funtion was assessed by 2D Echocardiograms in 33 patients, MUGA in 16 patients and by both in 4. Results: None of the patients had any symptom of CHF post HDCT. None developed a pericardial effusion. The median pre HDCT LVEF was 55% for the entire group (44% to 74%). The median post LVEF was also 55% (40% to 63%). An asymptomatic reduction in LVEF was observed in 15/53 patients (28.3%). In 3/15 the reduction was > 10%. In 9 the reduction was >5% and in 3 the reduction was < 5%. In these 12 patients who had a reduction in LVEF of >10% and >5% 5 received Melphalan alone and 7 received Cytoxan at 120 mg/kg. A pre HDCT LVEF < 55% was observed in 17 patients. There was no change post HDCT in 11 of these 17 patients. The post HDCT LVEF reduced by < 5% in 4 and >5% in 2. Again none of these patients was symptomatic. Conclusion: None of our HDCT patients developed cardiac symptoms upto 100 days post HDCT. Cytoxan 120 mg/kg and Melphalan 200 mg/m2 resulted in aymptomatic reductions of LVEF of between 5 and > 10% 100 days post HDCT.

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COMPARISON OF COMPLICATIONS AND LONGEVITY OF HICKMAN AND NEOSTAR CATHETERS IN STEM CELL TRANSPLANT RECIPIENTS

Pai, A.; Garner, P.; Dorr, S.; Akhtar, A.; Momin, F. Oakwood Hospital, Dearborn, MI

Purpose: To prospectively study the complications and longevity of tunneled Hickman and Neostar Catheters in auto, allo stem cell recipients and leukemic patients undergoing chemotherapy. Methods: Fifty Neostar and 38 Hickman catheters were studied. Neostar catheters can be used for stem cell collection and therefore were prefered in autografts. The wider bore Neostar catheter was inserted in autografts prior to stem cell mobilization and maintained through apheresis and the transplant course. Hickman catheters were used for allografts and patients undergoing chemotherapy for leukemia. All catheters were surgically inserted and subcutaneously tunneled in the OR. Both types of catheters were removed when the patient became transfusion independent and did not need IV infuaions. Indications for premature catheter removal were: a)catheter malfunction, b)Fungemia/gram -ve bacteremia, c) persistent bacteremia on antibiotics, d)tunnel infection, e) DVT and f)Luminal occlusions that could not be lysed by t-PA. All patients received oral quinolone and fluconazole for gut decontamination. Results: There were no gram negative or fungal infections in any patient. Gram+ bactermia and tunnel infection was significantly greater in Neostar group (40% and 4%) vs 30% and 0% in Hickman group. The median duration of Neostar and Hickman catheters were 45 days (9 - 170) and 75 days (19 - 78) days respectively. Premature removal of Neostar due to infection was 18% compared to 9.4% in Hickman group. Detailed results are shown in the table below, Conclusion: In our experience wide bore Neostar Catheters are associated with more infectious complications and have a shorter longevity compared to Hickman catheters. Intraluminal occlusions leading to premature removal are more frequent with Hickman catheters. Venous thrombosis occurred equally in both groups.

	Med. Duration, days	Gram + Bacteremia	Tunnel Infection	Removal due to Inf	Occlusions	Venous Thrombosis	Removal for occlusion
Neostar (n = 50)	46 (9 - 173)	20/50 (40%)	2/50 (4%)	9/50 (18%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Hickman (n = 39)	75 (19 - 180)	11/39 (28.2%)	0	3/39 (9.4%)	7/39 (20.5%)	2/39 (5.1%)	4/39 (10.2%)

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LOW DOSE DOPAMINE/HEPARIN FOR THE PRE-EMPTIVE TREATMENT OF VENO-OCCLUSIVE DISEASE OF THE LIVER IN PATIENTS RECEIVING BUSULFAN/CYCLOPHOSPHAMIDE AND ALLOGENEIC OR AUTOLOGOUS STEM CELL TRANSPLANTATION

Sivasubramaniam, V.; Dodds, S.; Lyman, G.H.; Hiemenz, J.; Maloy, B.; Morgalis, M.; Cirenza, E.; Ballester, O. Albany Medical Center, Albany, NY

Veno-occlusive disease (VOD) of the liver is recognized as a common complication of high-dose therapy and a major cause of morbidity and mortality. Various prophylactic approaches have suggested that the incidence of VOD could be decreased (from 40% to 15%) but this would require treating the entire patient population. We report here a prospective study evaluating the pre-emptive treatment of VOD, at the earliest detectable elevation of serum bilirubin and prior to the establishment of the full clinical syndrome. The protocol called for administration of dopamine at 2µg/kg/min and heparin infusion at 100 units/hour triggered by an elevation of total serum bilirubin ≥1.2 mg/dL within the first 20 days post transplant. From August 1994 -August 2001, 37 consecutive patients received Bu/Cy (Busulfan 16 mg/kg po over 4 days and cyclophosphamide 120 mg/m^2 over 2 days) followed by allogeneic (n=16) or autologous (n=21) stem cell rescue. Diagnosis included AML(n=10), NHL(n=9), HD(n=6), myeloma(n=5), others(n=7). The protocol was activated in 12 patients who met criteria on day + 6.5 (median) with a mean total bilirubin of 1.68 mg/dL at initiation of protocol. In these patients the mean peak value of total bilirubin rose to 3.23 mg/dL on day + 11 (median). Of these 12 patients 2 met criteria for VOD (McDonald, Hepatology, 1984). There was one episode of gastrointestinal bleed in the treated group during the first 100 days post-transplant. The non-treated group had one episode of hematuria. Overall, transplant related mortality during the first 100 days post transplant was 2.7% (1 death related to recurrence of AML). There were no deaths due to VOD or bleeding complications. In conclusion, our study reveals that pre-emptive treatment with heparin and dopamine instituted in 32% of the patients resulted in a low VOD incidence of 5.4%.

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FACTORS ASSOCIATED WITH INCREASED HOSPITAL COSTS IN PATIENTS TREATED WITH LIPID-BASED ANTI-FUNGAL THERAPY

Tong, K.B.[1]; Greenberg, R.N.[2]; Cagnoni, P.J.[3]; Wingard, J.R.[4]; Prendergast, M.M.[5] 1. Quorum Consulting, Inc., San Francisco, CA; 2. University of Kentucky, Lexington, KY; 3. University of Colorado Health Sciences Center, Denver, CO; 4. University of Florida College of Medicine, Gainesville, FL; 5. Fujisawa Healthcare, Inc., Deerfield, IL

BACKGROUND. A randomized, double-blind, comparative multi-center trial was conducted to compare liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC) for empirical anti-fungal therapy. The doses for L-AmB were 3 mg/kg per day and 5 mg/kg per day, and the dose for ABLC was 5 mg/kg per day. L-AmB was found to have a superior safety profile in febrile neutropenic patients compared to ABLC. Nephrotoxicity was significantly higher in ABLC patients. OBJECTIVES. The purpose of this analysis is to determine if other factors contribute to increased hospital costs and length of stay. METHODS. A retrospective analysis of 89 patients enrolled in the clinical study was performed to assess hospital costs and length of stay following the start of empirical anti-fungal therapy. Bivariate and multivariate regressions were performed to identify variables most likely to affect hospital costs and length of stay. RESULTS. Allogeneic BMT status, days of treatment, doubling of baseline creatinine, and dialysis were found to be predictive both of increased hospital costs and length of stay. Length of stay and number of concomitant nephrotoxic agents also were found to affect hospital costs. CONCLUSIONS. Overall, risk factors and clinical outcomes associated with nephrotoxicity increased hospital costs and length of stay in patients treated empirically with lipid-based anti-fungal agents. In conclusion, the determination of the optimal lipid-based agent for empirical anti-fungal therapy should incorporate both patient-specific risk factors and product-specific outcomes.

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ACUTE RENAL DYSFUNCTION ASSOCIATED WITH ANTITYHMOCYTE GLOBULIN IN THE CONDITIONING FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

Voltarelli, J.; Stracieri, A.; Coutinho, M.; Paton, E.; Almeida, K.; Vieira, O.; Dantas, M. BMT Unit, Hospital das Clinicas of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

We report two cases of acute renal dysfunction associated with the infusion of horse antithymocyte globulin (Lymphoglobuline, Sangstat, France) in the conditioning for stem cell transplantation. The first patient (26 y old, male) had severe aplastic anemia and was conditioned with cyclophosfamide (50mg/kg x4) and ATG (30 mg/kg x3). Hydrocortisone and dexchlorpheniramine were given before ATG. During the first dose, the patient developed fever, shaking, skin rash, abdominal pain, vomiting, hypotension (8 x 4 mmHg) and low urinary output. He was treated with steroids and the infusion was completed. In the next day, serum creatinine rose from 1.2 to 2.3 mg/dl, arterial tension dropped to 8 x 5, urinary output decreased and he was treated with dopamine and IV fluids. ATG was witheld and given in the next day producing fever and shaking. He was treated with hydrocortisone, the rest of the 2nd dose and the 3rd dose were given at slower rate without reactions. The second patient (26 y, m) received an autologous peripheral blood stem cell transplantation for lupus nephritis. Planned conditioning was CY 200 mg/kg plus ATG (15 mg/kg x6). During the 1st dose of ATG the patient developed skin rash, shaking and arterial hypertension (19 x 12 mmHg). Infusion was completed at slower rate. Creatinine rose from 1.7 to 2.1 and after the 2nd. dose of ATG blood pressure increased and urine output decreased until anuria. Creatinine rose to 4.5, arterial tension to 17 x 13, hemodialysis was performed and the CY dose was completed, but no further ATG was given. Renal function improved gradually and the patient was discharged on D+32. We hypothesize that release of cytokines by ATG caused renal dysfunction in our patients. We are aware of only one other similar case reported at Am J Kidn Dis 34:1155, 1999.

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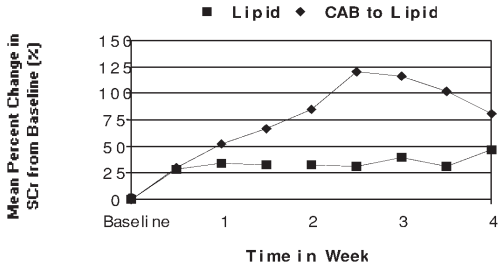
A MULTICENTER, RETROSPECTIVE STUDY OF AMPHOTERICIN B (AMB)-INDUCED NEPHROTOXICITY IN ADULT ALLOGENEIC HEMATOPOIETIC PROGENITOR CELL TRANSPLANT (HPCT) RECIPIENTS WITH INVASIVE FUNGAL INFECTIONS (IFI)

Waller, E.K.[1]; Miller, C.B.[2]; Chao, N.J.[3]; Annaissie, E.J.[4]; Fleck, P.R.[5]; Klingemann, H.[6]; Fruchtman, S.[7]; McGuirk, J.[8]; Cagnoni, P.J.[9]; McSweeney, P.[9] 1. Emory University, Atlanta, GA; 2. Johns Hopkins University, Baltimore, MD; 3. Duke University Medical Center, Durham, NC; 4. University of Arkansas Medical School, Little Rock, AR; 5. Cincinnati Transplant Institute, Cincinnati, OH; 6. Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; 7. Mount Sinai Medical Center, New York, NY; 8. Oncology & Hematology Associates of Kansas City, Kansas City, MO; 9. University of Colorado Health Sciences Center, Denver, CO

AMB remains the drug of choice for IFI in adult HPCT recipients. Lipid AMB formulations (LIPID) are less nephrotoxic than conventional AMB (CAB), but there is still a controversy regarding when LIPID therapy should be initiated. A multicenter, retrospective chart review of 87 adult allogeneic HPCT recipients was conducted in 8 centers between 1995-2000. Thirty-three patients were intiated on CAB (mean dose 0.7±0.3 mg/kg/day) and 54 were initiated on LIPID (mean dose 4.9±1.9 mg/kg/day) for proven or possible IFI. There were no significant differences in baseline demographics between the two treatment groups, however LIPID patients had a significantly higher mean baseline serum creatinine (SCr) compared

to CAB patients (1.11±0.69 vs. 1.44±0.92 mg/dL, p<0.01). Following initiation of therapy, 64% of CAB patients required conversion to a LIPID (median of 4 days), while 22% of patients initiated on a LIPID were converted to another LIPID (p<0.001). Nephrotoxicity accounted for 81% of CAB patient conversions. The figure below shows significantly more nephrotoxicity among patients initiated on CAB then subsequently switched to LIPID compared to patients initially treated with LIPID (p<0.05 comparing percent change in SCr from week 1 to week 4). Significantly more patients who were converted from CAB to LIPID experienced a doubling in SCr compared to patients initially treated with LIPID (p=0.04). 6/33 (18%) patients started on CAB remained on initial therapy at week 4, compared to 29/54 (54%) patients who received initial therapy with LIPID. Insert Figure here Conclusion: Initial therapy with CAB in HPCT recipients resulted in the majority being switched to LIPID due to nephrotoxicity. The strategy of starting CAB and switching to LIPID did not result in an improvement in nephrotoxicity compared to initiating patients on LIPID (p<0.05). Initiating antifungal therapy with LIPID limits nephrotoxicity in allogeneic HPCT recipients.



	Week				
	Baseline	1	2	3	4
Initial CAB/CAB to LIPID	33/0	12/21	12/19	10/16	6/11
Initial LIPID	54	54	53	40	29

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GRANISETRON VERSUS ONDANSETRON IN THE PREVENTION OF NAUSEA AND VOMITING IN BONE MARROW TRANSPLANT PATIENTS: RESULTS OF A PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED TRIAL

Walsh, T.L.[1,2]; Valley, A.W.[1,2]; Holle, L.M.[1,2]; Morris, A.K.[1,2]; Callander, N.S.[1,2]; Freytes, C.[1,2]; Bradshaw, P.[2]; Clark, G.[2] 1. South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio, TX; 2. University of Texas Health Science Center, San Antonio, TX

The 5HT3 antagonists represent a significant advance in the prevention of acute nausea and vomiting from highly emetogenic chemotherapy. The majority of conditioning regimens for bone marrow transplantation(BMT) are highly emetogenic and 5HT3 antagonists, in combination with other antiemetics, have been incorporated as the standard of care for prevention of nausea and vomiting in this setting. At our institution, the standard prophylactic antiemetic regimen at the time of study initiation included intravenous ondansetron as the chosen 5HT3 antagonist. However, with the advent of granisetron, another 5HT3 antagonist, we sought to determine if there were any differences in efficacy or toxicity between these 2 agents during conditioning therapy for autologous BMT. A total of 110 patients were randomized(96 evaluable) to receive either ondansetron 0.15 mg/kg IV Q8H or granisetron 10 mcg/kg IV QD. Additionally, both treatment groups received dexamethasone 10 mg IV QD and lorazepam 1 mg IV Q8H. Antiemetic prophylaxis was continued until 24 hours after completion of chemotherapy. Nausea and distress were measured subjectively with visual analog scales and emetic episodes were quantified. Patient demographics and risk factors for nausea/vomiting were similar between treatment groups. In the granisetron group(n=46), 48% experienced none-mild nausea and 52% experienced moderate-severe nausea. The ondansetron patients(n=50) had similar results with a 50% incidence in each category(p=0.841; Fisher's exact test). The median number of emetic episodes for granisetron and ondansetron was 3(range 0-15) and 1(range 0-9) respectively, (p=0.228; Wilcoxon rank-sum). The overall incidence of adverse effects were also similar for ondansetron and granisetron(p = 0.294; Wilcoxon rank-sum), and no patient prematurely discontinued the study because of severe toxicities. This study confirms that ondansetron and granisetron are equally effective and safe in the prevention of acute nausea and vomiting associated with conditioning therapy for autologous BMT. The agent of choice should be based on institutional cost.

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BUGSLUG: ANALYSIS OF EPIDEMIOLOGY AND DRUG SUSCEPTIBILITY DATA UTILIZING A RELATIONAL DATABASE

White, M.[2]; Lyons, E.[2]; Mann, L.[1]; Pineiro, L.[1,2]; Vance, E.[1,2]; Berryman, B.[1,2]; Fay, J.[1,2]; Agura, E.[1,2] 1. Baylor University Medical Center, Dallas, TX; 2. Baylor-Sammons Cancer Center, TOPA, Dallas, TX

The BugSlug database is a relational database created using Microsoft's Access-97 program. Tables in the database include: patient information, culture information (separate bacterial, fungal, and viral tables), graft-versus-host disease data, and drug susceptibility information. Data is obtained from the BMT program clinical database and reports from Baylor University Medical Center's Microbiology Department. Data is analyzed on a quarterly basis. Types of data entered include: diagnosis, preparative regimen, type and date of graft, date of culture, type of culture, and pathogen, among others. If the particular culture is tested for drug susceptibility, each drug tested against the pathogen is statused as "Resistant", "Intermediate", "Susceptible", or "Not Tested". Regular analyses of data include: number of unique patient isolates per type of culture, unique positive bacterial and fungal isolates (per drug susceptibility) per month, incidence of positive CMV antigenemia per month by disease and type of transplant, types of bacterial and fungal organisms isolated per source of culture, incidence of common organisms per month, drug resistance patterns for bacterial and fungal isolates, Vancomycin-resistant Enterococcus resistance patterns per drug tested, common bacterial and fungal organisms per graft, and unique positive cultures at day post transplant. Correlation with incidence of graft versus host disease and correlation with patient and donor pre-transplant CMV status is also performed. Findings are presented quarterly at BMT physicians' meeting for review and modification of standard prophylactic and prevention practices. The minutes of the physicians' meeting document continuing quality assurance efforts of program as required by FAHCT standards.